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Interview with Dr Sarah Coulthurst

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Sarah Coulthurst is a Wellcome Trust Senior Research Fellow based in the School of Life Sciences at the University of Dundee, UK. She is a molecular bacteriologist with long-standing interests in protein secretion systems and inter-bacterial interactions, both co-operative and competitive. Her current research is mainly focused on the Type VI secretion system, a protein 'nanoweapon' used by many bacteria to deliver toxic effector proteins into other cells. Her group aims to understand how this system effectively delivers effectors into bacterial and fungal competitors, and to elucidate the mode of action of the effectors and their impact on targeted cells and populations. Her contributions have been recognised through the award of the Microbiology Society Fleming Prize, the Society for Applied Microbiology W. H. Pierce Prize, and the Royal Society of Edinburgh Patrick Neill Medal.

1. What is your research background - what did you first start working on at the beginning of your academic career?

Throughout most of my school career I liked everything, and enjoyed English literature, history and art as much as science and maths. At sixteen, when I had to specialise, I went for Science-based subjects because I knew that I wanted to go in that direction at University. I think that perhaps these broader early interests are why I still really enjoy the many creative and communication-based aspects of my work. I studied for a Natural Sciences degree at the University of Cambridge, specialising in Biochemistry. As part of this, I did a Masters project in the Peter Leadlay group on polyketide synthases (macromolecular enzyme assemblies that produce many important antibiotics and other natural products). After that, I completed a PhD degree with George Salmond, studying quorum sensing (inter-bacterial chemical communication).

2. Have you always wanted to work in academia?

No! I very nearly trained to be a doctor. Then I decided I was more interested in medical research and decided to undertake a basic science degree. Although I really enjoyed my degree and was fascinated by all the science I learned, practical classes actually put me off bench work and I decided to look outside academia. But then I had the chance to do an integrated Masters in my 4th year, did an extended project in an academic lab, and loved it! So I decided to do a PhD and began to realise that academic research was the route I really wanted to follow.

In terms of area, I was always more interested in microbiology than things like cancer biology – but I do want to make a difference to human health. Understanding and mitigating the effects of infectious diseases is one of the world's most difficult and pressing problems. So studying microbes is a great route to achieving this.

3. How has your early work brought you to what you are working on now?

Protein secretion systems and inter-bacterial interactions have been recurring themes in my career. As an undergraduate, I was inspired by lectures about antibiotic production by

bacteria (bugs killing bugs), bacterial communication (bugs co-operating with bugs) and how bacteria interact with the environment and other cells using sophisticated machines (secretion systems). Much credit here must go to George Salmond, who went from giving most of these lectures to being my PhD supervisor and long-standing mentor. My PhD was on quorum sensing (QS) and included how QS systems regulate antibiotic production and secretion. I then did a first postdoc working on a combination of QS and bacterial secretion systems, and moved to Dundee to do a second with Frank Sargent, where I learned more about biochemistry as well as protein translocation. When I set up my own lab, I chose to work on a new (at the time) protein secretion system - the Type VI secretion system (T6SS), using my experience in secretion systems and in opportunistic enteric bacteria, in which T6SSs had not yet been studied. In the early days, it was thought that the T6SS was used to attack eukaryotic host organisms. When it became clear that many T6SSs, including that of our model, *Serratia marcescens*, are used against bacterial competitors, this was fantastic for me. It fitted well with my background in inter-bacterial interactions and bacterial competition via antimicrobial secondary metabolites (which we have done some work on too).

4. What first attracted you to your field?

I have always found molecular microbiology fascinating - all of the amazing and complex things that bacteria can do (and other microbes of course, as I am increasingly finding out). The combination of incredible fundamental biology with the vital need to understand how these bugs can cause disease so efficiently, with the hope eventually to prevent this, was compelling, and remains so. We really need to understand the basic mechanisms of how pathogenic microbes succeed and cause disease in order to try and find new strategies to control them. The bacterial T6SS is one example of a highly evolved and very effective machinery used in microbiological warfare. By learning about this ‘weapon’ and other tricks bacteria use to kill rival microbes, hopefully we can exploit the knowledge to find new ways of combating infectious diseases.

5. What do you think the most interesting questions are at the moment in your field?

I think that there a number of really interesting questions in the T6SS field; here I will just mention three. Firstly, can the T6SS be used against Gram-positive bacteria? If not, as so far seems to be the case, then why not, given that it can be used against such a variety of other targets (diverse Gram-negative bacteria, fungal cells, amoebae and animal cells)? Second, what are the roles and importance of T6SSs in different types of real human-associated (and other) microbial communities? Finally, can we harness T6SSs for use as biocontrol/direct anti-bacterial agents for translational or therapeutic purposes?

6. Where do you think microbiology is heading in the future? What do we need to be thinking about?

The ready availability of whole genome sequencing represents a step change and offers huge opportunities. These include great advances in our ability to understand bacterial infections

and a new ability to shift from model organism-based research to studies of real-life environments and microbes. However it also provides huge challenges in terms of the requirement for appropriate accompanying data analysis. I also think it is very important not to lose sight of the fact that, whilst it is now very easy to sequence even large numbers of strains, these studies, like any other, should still be performed with a clearly defined hypothesis or aim.

I think that another very important shift currently underway is a widely increasing appreciation that that microbes generally exist in mixed populations and in challenging, non-uniform environments. Whilst model systems and controlled conditions remain critical for fundamental understanding of basic processes, we must also consider our work in the context of complex real-life environments. Finally, I think that a really exciting and growing area in bacteriology is understanding the evolutionary influence of phages and phage-resistance mechanisms and the role they both play in determining population structures. This then extends into considering the future possibilities and challenges of phage therapy, particularly given current advances in synthetic biology.

7. What do you enjoy the most about your work? And what about the least?

What I enjoy most about my work is the science itself – the excitement of a new finding or the satisfaction of a beautiful set of data that confirm a hypothesis. I also like meeting and working with lots of very different and smart people, and enjoy the processes of making figures, presenting data and writing papers. The things I enjoy least are some of the necessary administration and other tasks that distract from the more directly research related ones, and also when someone in the lab is working very hard and doing all the right things, but the experimental 'break' just doesn't come. I wish I could have a magic wand!

8. Academia is known for being challenging in terms of high workloads and long hours - how do you strive to achieve a work-life balance?

With two children (aged seven and three), it is impossible not to have a balance, but it isn't always easy. I think that you need to somehow find the arrangements that work for you and your family, and to not be too tough on yourself. It is hard not to feel you aren't being the best parent or scientist, but I think that most people in my situation do a pretty good job at both! Being a parent helps to put work in perspective and ensures you do plenty of non-work activities. We all want our kids and students to be able to follow their career dreams and have a happy family, so it is good to hopefully provide some kind of model for doing this. Having said that, I'm very glad we live in an age where I can catch up with work at any time and place and so have some flexibility; this is central to making things work. Having the support of great colleagues also makes a big difference.

9. What has been the most surprising result you've had in your career so far?

It is easiest to think of two recent ones. We were surprised to find that a new antibacterial toxin has highly selective ion channel forming properties in membranes, when we had been

expecting it to form very non-specific pores. We were also not expecting our 'anti-bacterial' Type VI secretion system to target fungal cells using specific effectors, although I think in hindsight we shouldn't have been surprised at all!

10. What advice would you give to other early career researchers starting out in their career given your experiences?

(1) Don't be scared to talk to editors or grants advisers/programme managers if you receive a decision or requests that you truly think are incorrect or unreasonable, or before (re-)submitting a paper or grant application. Sleep on it first, be polite and be prepared to listen. But also be willing to accept that no one is successful every time, learn what you can, and try not to take it personally.
(2) Particularly at the start of an independent career, always seek feedback on your grant applications from people who know the funder and people who aren't very familiar with your precise area of research.
(3) Remember that your trainees won't necessarily think in the same way as you do.

11. What has been your most rewarding experience so far? Why?

The most rewarding experience, for me, is to see trainees, especially PhD students, develop into mature and confident researchers. The day that a student turns round and (correctly) tells you why your suggestion is not the best one, or spots the killer control experiment, is always a great moment, and PhD vivas are proud days. It is also a great feeling to see work you are very proud of being published and then cited by other people.